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Gefitinib Treatment Is Highly Effective in Non-Small-Cell Lung Cancer Patients Failing Previous Chemotherapy in Taiwan: A Prospective Phase II Study

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Summary

Gefitinib has shown activity in the treatment of non-small-cell lung cancer (NSCLC) patients who failed previous platinum-based combination chemotherapy and/or taxane treatment. Recently, gefitinib was documented to be more effective in an East Asian population, as well. Thus, we performed a gefitinib trial in Taiwanese patients to assess the efficacy of this regimen.

Treatment consisted of gefitinib 250 mg one tablet daily until disease progression.

Thirty-six patients were enrolled from January 2003 to September 2004. Gefitinib was second-line treatment in 10, third-line in 15, fourth-line in 9, and fifth-line in 2. All patients were evaluable for toxicity profile and response rate. After 8 weeks of treatment, three patients had a complete response (CR) and nine had a partial response (PR), with an overall response rate of 33.3% (95% confidence interval 17.9% - 48.7%). All treatment-related toxicities were few and mild in severity, except that one patient suffered from reversible grade 3 interstitial pneumonitis. The median time to disease progression was 4.7 months, and the median survival was 9.5 months. The one-year survival rate was 45.1%. Survival was significantly better in those who responded to treatment (CR and PR) than in those who did not (median 20.1 *vs.* 4.7 months, p=0.0002). Survival was also better in those who demonstrated disease control using gefitinib (CR, PR, and stable disease) than in those who did not (14.1 *vs.* 1.4 months, p<0.0001).

The authors conclude that daily gefitinib treatment has high activity, is well tolerated, and provides very good survival in Taiwanese NSCLC patients who have failed previous chemotherapy, especially in those who responded to gefitinib treatment or those whose disease was controlled by gefitinib treatment.

Key words: **Epidermal growth factor receptor (EGFR), gefitinib, non-small cell lung cancer, salvage therapy.**

INTRODUCTION

Gefitinib (Iressa; AstraZeneca Pharmaceuticals, Wilmington, DE) is a selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). It is an orally active agent for advanced non-small-cell lung cancer (NSCLC) in those who have failed a previous platinum-based regimen and taxane treatment [1-3]. In two large phase II trials (IDEAL 1 and IDEAL 2), gefitinib was shown to have substantial effect as salvage treatment for patients who had failed at least one or two previous regimens of chemotherapy [1,2].

The IDEAL 1 study found that Japanese patients had a better response to gefitinib treatment than Caucasian patients. Once it was found that the

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EGFR mutation occurred more frequently in Japanese patients than in Caucasians, and that those patients with an EGFR mutation had a better response to gefitinib treatment, researchers understood why gefitinib had better efficacy in Japanese patients than in Caucasians [4-6].

Based on the relatively good toxicity profiles and high activity found in the Japanese patients of the IDEAL-1 study, we decided to conduct a phase II trial using single-agent gefitinib in NSCLC patients failing previous chemotherapy, in order to investigate the efficacy and toxicity profile of this agent in Chinese patients who lived in Taiwan.

PATIENTS AND METHODS

The study was conducted according to existing rules for good clinical practice, and the study protocol was approved by the local ethics committee. Patients with NSCLC who had failed previous platinum-based chemotherapy (age ≤80 years) or non-platinum-based chemotherapy (age >80 years), were entered into the study after giving informed consent. Eligibility criteria were: a histological or cytological diagnosis of stage IV NSCLC in those who had failed previous chemotherapy; clinically measurable disease, defined as bidimensionally measurable lesions; no previous radiotherapy on measurable lesion(s); and a life expectancy of more than 2 weeks. Adequate bone marrow reserve and renal and liver functions, which are usually required in clinical trials with chemotherapy, were not required in the present study.

Baseline evaluations included a documentation of the patient's history, a physical examination, and a performance score. A complete blood cell count, urinalysis, serum biochemistry profile, ECG, chest roentgenography, whole body bone scan, brain CT scan, and chest (including the liver and adrenal glands) CT scan were also performed.

Subsequent complete blood cell count and serum biochemistry studies were performed 2 weeks after the beginning of gefitinib treatment, and then, every 4 weeks. Study drug-related adverse events and toxicities were recorded, according to established Eastern Cooperative Oncology Group (ECOG) criteria [7].

All patients received gefitinib at a fixed daily oral dose of 250 mg. Concomitant use of other chemotherapeutic agents was not allowed. Palliative radiotherapy to the lesion not used as a measurable lesion(s) was allowed. Gefitinib was given until disease progression or the presence of intolerable toxicity. Treatment was temporarily stopped for one or two weeks if the patients suffered from grade 3 or worse toxicities; gefitinib could be re-started from a 50% dose once the toxicity was reduced to grade 2 or less, except in cases of drug-induced pneumonitis, in which the treatment would be permanently stopped if the patient suffered from grade 3 or worse toxicity. A subsequent dose escalation to the original level was allowed provided that the patient tolerated the doses given at the 50% level.

Evaluation of response was performed after 4 weeks of treatment, and every 8 weeks thereafter. Types of response were also assessed, according to established ECOG criteria [7]. Responding patients and those with stable disease were continued until disease progression.

A Simon two-stage phase II minimax design was used (α=0.1, β=0.1) to estimate patient accrual targets. It was estimated that the power of this study to detect a true response rate of 20% was 0.9, requiring an accrual of at least 32 patients [8]. Survival was measured from administration of the first dose until the date of death or last follow-up. For statistical analysis, the Kaplan-Meier method with a log-rank test was used for single-variate survival analysis. The Cox-regression test, including sex, smoking, response to treatment or not, adenocarcinoma or others, performance status, and present treatment as ≤ third-line or later, was performed for multivariate survival analysis. The SPSS statistical program was used.

RESULTS

Between January 2003 and September 2004, 36 patients (20 males, 16 females) were enrolled into this study. The mean age was 62 years, with a range of 35-82 years. Seventy-five percent of the patients had a performance status of 2 or worse. All were stage IV patients. For those who received gefitinib as third-line or later treatment, cisplatin-based combination chemotherapy was given as first-line treatment and docetaxel as second-line treatment. The patients' clinical characteristics are shown in *Table 1*. All were assessable for toxicity profile and treatment response.

The mean number of treatment days was 223 (median 140 days, range 8-779 days). After 8 weeks of treatment, three patients had a complete response (CR) and nine patients had a partial response (PR), with an overall response rate of 33.3% (95% confidence interval 17.9% - 48.7%). Stable disease was found in 14 patients (38.9%), and progressive disease was documented in the remaining 10 (27.8%).

The median time to disease progression was 4.7 months (95% confidence interval 0-10.6 months), and median survival was 9.5 months (95% confidence interval 4.1-14.9 months). The one-year survival rate was 45.1%. Survival was significantly better in those who responded to treatment (CR and PR) than in those who did not (*Figure 1*, median 20.1 *vs.* 4.7 months, p=0.0002). Survival was better in those who had disease control due to gefitinib treatment (CR, PR, and stable disease) than in those

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TABLE 1 - *Patient characteristics (n=36).*

Variable		N.	%
Male/female		20/16	55.6/44.4
Mean age, Yr (range)		62 (35-82)	
Smoking, yes/no		14/22	38.9/61.1
WHO performance status	1	9	25
	2	21	58.3
	3	5	13.9
	4	1	2.8
Histology	Adenocarcinoma	25	69.4
	Squamous cell carcinoma	5	13.9
	NSCLC, type unspecified*	6	16.7
Present treatment as	2nd line	10	27.8
	3rd line	15	41.7
	4th line	9	25
	5th line	2	5.6

*"NSCLC, type unspecified" means the pathologist could only make the diagnosis of NSCLC. However, further sub-classification was too difficult to make.

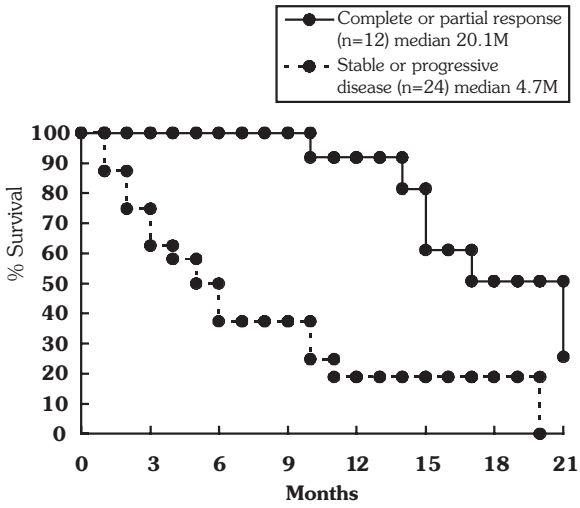

FIGURE 1 - The Kaplan-Meier survival curve of 12 patients with complete or partial response versus 24 patients who had stable or progressive disease after treatment. The median survival was 20.1 months and 4.7 months, respectively (p=0.0002).

who did not (median 14.1 *vs* 1.4 months, p<0.0001), and was also better in those patients who had a better performance status (p=0.0014). Survival was longer in females and non-smokers, however, without statistical significance, and survival was not related to histology or present treatment as ≤ third line or later (*Table 2*). Survival was also better in those who had stable disease after gefitinib treatment than in those with progressive disease in spite of treatment (*Figure 2*, median 9.4 *vs* 1.4 months, p=0.0011). The Cox-regression test for multivariate analysis, including sex, smoking, response to treatment or not, adenocarcinoma or others, performance status, and present treatment as ≤ third-line or later, showed that only response to treatment (p=0.0003) and performance status (p=0.0001) had statistical significance.

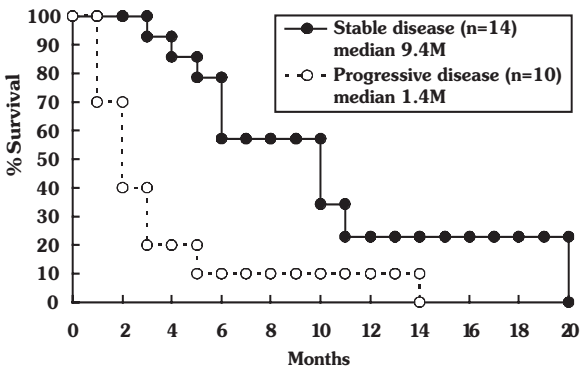

FIGURE 2 - The Kaplan-Meier survival curve of 14 patients who had stable disease versus 10 patients who had disease progression. The median survival was 9.4 months and 1.4 months, respectively (p=0.0011).

All patients enrolled into the study were eligible for toxicity evaluation. The toxicities were few and mild in severity. No more than grade 2 toxicity

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TABLE 2 - *Survival status of the patients treated with gefitinib.*

		N. Patients	Median survival (months)	*p* value (log-rank)
Sex	Male	20	9.3	0.3914
	Female	16	13.7	
Smoking or not	Yes	14	3.4	0.2022
	No	22	13.7	
Histology	Adenocarcinoma	25	9.4	0.4176
	Non-adenocarcinoma	11	13	
Response or not*	Yes	12	20.1	0.0002
	No	24	4.7	
Disease controlled or not#	Yes			<0.0001
	No	26	14.1	
		10	1.4	
Performance status	1	9	20.1	0.0014
	2	21	5.1	
	3	5	4.7	
	4	1	16.5	
Present treatment as	≤ 3rd line	25	9.3	0.7441
	≥ 4th line	11	13.9	
Skin rash	Yes	12	19.1	0.011
	No	24	5.1	
Dry skin	Yes	8	26	0.0065
	No	28	5.1	

*complete response and partial response.
#complete response, partial response, and stable disease.

occurred in the present study, except for one patient with grade 3 drug-induced interstitial pneumonitis. This patient responded well to steroid treatment. Other toxicity profiles included skin rash: ten grade 1, and two grade 2; dry skin: two grade 1, and six grade 2; liver enzyme elevation: one grade 1, and one grade 2; diarrhea: four grade 1, and four grade 2; and paronychia in 4. The response rate was higher in those with skin rash (p=0.0295) and dry skin ($p<0.001$), but not in those with paronychia (p=0.064). Survival was significantly better in those with skin rash (n=12, median 19.1 months) versus those without skin rash (n=24, median 5.1 months) (p=0.011). Survival was also better in those with dry skin (n=8, median 26 months) versus those without dry skin (n=28, median 5.1 months) (p=0.0065), but was not correlated with the occurrence of paronychia or not (p=0.1853).

DISCUSSION

Because the chemotherapy response rate for those who have failed previous chemotherapy is usually low, at a level at or below 20%, the options available to patients with advanced NSCLC resistant or refractory to first-line chemotherapy are very limited. The only chemotherapeutic agents that have been documented in phase III studies to be effective in second-line treatment were docetaxel and pemetrexed [9,10]. In contrast, EGFR-TKI is a new class of anti-cancer agents that has been found effective, since 2003, in the salvage treatment of NSCLC patients who failed previous chemotherapy, including tarceva in second-line treatment [11] and gefinitib for patients after failure with both platinum-based and docetaxel chemotherapies [2,3].

After a series of clinical trial reports and laboratory studies, it was found that female gender, nonsmoker, adenocarcinoma (especially those with a bronchioloalveolar carcinoma component), EGFR mutation, and East Asian ethnicity were known factors predicting a better response to EGFR-TKI treatment, including gefitinib and tarceva [4,5,12]. A previous study also found that response to gefitinib treatment predicted a better survival [12], as in this study.

The toxicity of gefitinib has been minimal and mild in degree, in both previous studies and this one [1,2]. The median survival and one-year survival of patients in this study was better than in the IDEAL-1 and IDEAL-2 studies. Gefitinib has the advantage of a relatively rapid tumor response and a lot fewer severe side effects. In the IDEAL-1 study, 68% of NSCLC patients met the criteria for objective

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